CHAPTER 66

Psychobiological and Pharmacological Approaches to Treatment

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Introduction

Posttraumatic stress disorder appears to be associated with a complex array of abnormalities in several biological systems. Despite the fact that systematic research in this area is at a relatively early stage, robust findings from a number of experimental approaches suggest that PTSD patients exhibit distinctive physiological, neuropharmacological, and neuroendocrinological alterations. In addition, there is a wealth of psychological and neurobiological theory and data that may be directly applicable to our understanding of PTSD. Moreover, unlike most other psychiatric disorders, there are several animal models that may be directly applicable to PTSD, including conditioned fear (Kolb, 1987, 1988), two-factor theory (Keane, Zimering, & Caddell, 1985), learned helplessness to inescapable shock (van der Kolk, Greenberg, Boyd, & Krystal, 1985), and kindling (Friedman, 1988, 1991; van der Kolk, 1987).

In my opinion, psychobiological laboratory techniques designed to elucidate the pathophysiology of this disorder will also lead to the development of clinically useful biological approaches to the diagnosis and treatment of PTSD. Although diagnostic and methodological considerations must be factored into any interpretation of such data, current biological research findings have fostered a growing conviction among many clinicians that pharmacotherapy is sometimes useful in reversing the biological abnormalities associated with PTSD.

In this chapter, I will begin by describing the physiological, neuropharmacological, and neuroendocrine abnormalities that current research suggests are associated with PTSD. This should provide a background for understanding and predicting why certain pharmacological approaches might be more effective than others in treating this disorder. Along the way, I'll point out some methodological problems with these research findings and how such problems limit the generalizability of current data on the pathophysiology of PTSD. I will then move on to clinical pharmacology *per se* and review current research findings on antidepressants, anxiolytics, carbamazepine, lithium, and neuroleptics. Finally, I'll discuss the widespread clinical phenomenon of chemical abuse/dependency among PTSD patients and argue that high co-morbidity rates between PTSD and chemical abuse/dependency may have a neurobiological basis which, in turn, has significant implications for treatment.

Physiological and Neurohumoral/Neuroendocrinological Alterations in PTSD

As shown in Table 66.1, physiological findings with PTSD patients (most of whom so tested are male Vietnam combat veterans) suggest that the homeostat for both the central and the autonomic nervous systems has been set at a level of higher arousal. Pulse rate and blood pressure appear to be elevated in the resting state, and PTSD patients exhibit greater cardiovascular arousal following exposure to either a neutral stimulus (white noise) or to a meaningful traumatomimetic stimulus,

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disordered patients (Charney, Woods, Goodman, & Henninger, 1987). Preliminary experiments with yohimbine at the National Center for PTSD (Southwick, Krystal, & Charney, 1989) indicate that after Vietnam veterans with PTSD receive this drug, they respond with hyperarousal, anxiety, panic, and intrusive recollections of traumatic combat experiences. In some patients, yohimbine appeared to elicit frank flashback (dissociative) episodes. If these results can be replicated, the fact that such a specific pharmacological probe can precipitate such specific trauma-related symptoms strongly implicates the central adrenergic system in the pathophysiology of PTSD.

HPA abnormalities have also been shown in combat veterans with PTSD. Urinary free cortisol levels are significantly lower among PTSD patients than among other psychiatric diagnostic groups (Mason *et al.*, 1986). Furthermore, PTSD patients exhibit a blunted ACTH (adrenocorticotropin hormone) response to CRH (corticotropin-releasing hormone) in contrast to normal controls (Smith *et al.*, 1989). (CRH is the hypothalamic hormone that stimulates the release of ACTH from the pituitary gland.) Both findings suggest that PTSD is associated with HPA axis hypofunction. Such an interpretation, however, may not do justice to complex HPA axis abnormalities which may include both tonic and episodic components and which may also depend upon the recency of exposure to traumatomimetic stimuli.

Reports of lower pain thresholds (Perry *et al.*, 1987) and increased susceptibility to chronic pain (Benedikt & Kolb, 1986; Rapaport, 1987) among PTSD patients suggest that this disorder is associated with lower available levels of endogenous opioids. Consistent with this possibility is a finding by Hoffman, Burges Watson, Wilson, and Montgomery (1989) who found lower beta-endorphin levels among combat veterans with PTSD. Paradoxically, although opioid levels appear to be reduced in the resting state, the pain threshold may become elevated after exposure to traumatomimetic stimuli. Pitman, van der Kolk, Orr, and Greenberg (1990) exposed Vietnam veterans with PTSD to combat scenes from the movie *Platoon*. They found that pain thresholds increased significantly after such exposure. This response, which they believe is a clinical example of what psychologists call *stress induced analgesia* (SIA), results from a sudden increase in opioid levels following exposure to stressful stimulation. Moreover, Pitman and co-workers were able to prevent the development of SIA by pretreatment with naloxone, the narcotic antagonist, indicating that SIA mediated by the endogenous opioid system is dysregulated in PTSD. Such dysregulation of the opioid system in PTSD may, in effect, represent a biological coping strategy. Van der Kolk, Pitman, Orr, and Greenberg (1989) suggested that endogenous opioids are released to attenuate the extreme arousal triggered by traumatomimetic stimuli. To go one step further, these investigators hypothesized that endogenous opioid fluctuations may serve as the biological vehicle for some of the avoidant/numbing symptoms associated with PTSD. They have shown that PTSD patients who are exposed to traumatomimetic stimuli exhibit greater anxiety, anger, guilt, and dysphoria following injection of naloxone, than following a placebo.

Finally, since the adrenergic, HPA, and opioid systems are related to one another through a variety of neuropharmacological feedback loops and since many experimental analogues to PTSD abnormalities can be reproduced in laboratory animals exposed to inescapable shock, there is growing confidence in some circles that the complex puzzle of PTSD's pathophysiology will be solved by further experimentation.

Methodological Considerations

Before progressing from basic biological research to clinical psychopharmacology, it is necessary to sound the cautionary notes that follow:

1. Results are few and far between. Except for sympathetic/adrenergic arousal (and perhaps heightened startle responses) most findings have not been replicated by many investigators. In addition, some findings are controversial; especially with regard to alterations in sleep and in HPA function.
2. Some studies report only baseline (i.e., catecholamine or cortisol) results in PTSD patients. Others obtain their measurements after exposure to neutral (i.e., white noise) stimulation. Others obtain biological measurements after exposing patients to traumatomimetic stimuli. Whereas still others have different combinations of the above procedures in their experimental protocols. Certainly, such findings are interesting snapshots of PTSD physiology but will remain difficult to interpret without more global information on the biological manifestations of PTSD in all three conditions. Future studies should compare baseline conditions with those provoked by physiological, pharmacological, and/or psychological provocation.
3. Research conducted to date has not controlled adequately for different diagnoses associated with PTSD that may seriously confound interpretation of experimental results. For example, depression is often associated with PTSD. Depression is a disorder that is known to be associated with abnormal sleep and HPA function. Therefore, experiments must be designed with adequate control groups in order to clarify whether observed sleep and HPA abnormalities are associated with PTSD alone, with depression alone, or with some biological hybrid when the two disorders occur simultaneously in the same individual. Finally, we must determine whether the depression associated with PTSD is a true major depressive disorder (according to the DSM-III-R) or whether it is (biologically) a qualitatively different type of depression/dysthymia that represents a specific affective subtype of PTSD (Friedman, 1990).
4. Almost all quantitative biological research has been conducted on male Vietnam combat veterans. Studies with female war zone veterans are needed to determine whether current findings are gender-specific. Furthermore, quantitative data are needed on male and female survivors of other types of traumatization before we can extrapolate from the current results to other groups of survivors.
5. We must acknowledge the pessimistic possibility that unraveling the pathophysiology of PTSD may not necessarily help us discover an effective drug for treating this disorder. The complex interrelationships

Table 66.1. Physiological Alterations Associated with PTSD

Sympathetic hyperarousal
Tonic—resetting of the homeostat at a higher level
Episodic—in response to neutral stimuli
Episodic—in response to traumatomimetic stimuli
Excessive startle reflex
Lowered threshold
Increased amplitude
A reducer pattern of cortical evoked potentials in response to neutral stimuli
Abnormalities in sleep physiology
↑ Sleep latency, ↓ sleep time, ↑ movements, ↑ awakenings
Disturbances in sleep architecture
Traumatic nightmares differ from other types of nightmares

such as the sounds or images of combat (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Kolb, 1987; Malloy, Fairbank, & Keane, 1983; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987). The startle response to neutral stimuli in children and in adults indicates that PTSD patients, in contrast to appropriate controls, exhibit a lower startle threshold as well as a significant enhancement of the startle response itself (Ornitz & Pynoos, 1989; Paige, Reid, Allen, & Newton, 1990).

Paige *et al.* (1990) reported robust differences between PTSD patients and others with respect to the pattern of cortical evoked potentials recorded in response to a stimulus pulse of white noise. PTSD patients showed significant responses to sound intensities that were at or below threshold for most normal subjects. Furthermore, the pattern of cortical evoked potentials elicited by auditory stimuli in PTSD patients showed a reduced rather than an augmented electrical pattern. Interpreting these findings in the context of the augmenting/reducing literature (Buchsbaum, 1976), Paige *et al.* (1990) suggested that PTSD patients are "reducers" in whom inhibitory feedback loops are activated to dampen a tonic state of hyperarousal.

Finally, sleep and dreaming are altered in PTSD. PTSD patients have difficulty initiating and maintaining sleep. Several studies indicate marked disruption of sleep architecture in PTSD exemplified by increased Stage 1, increased Stage 2, decreased Delta sleep, increased rapid eye movement latency, and decreased total REM percentage (Friedman, 1988; Kramer & Kinney, 1985; Lavie, Hefez, Halperin, & Enoch, 1979; Schlossberg & Benjamin, 1978). Other studies have failed to find such abnormalities (Greenberg, Pearlman, & Gampel, 1972; Kauffman, Reist, Djenderedjian, *et al.*, 1987; Ross, Ball, Sullivan, & Caroff, 1989; W. Van Kammen, Christiansen, D. Van Kammen, & Reynolds, 1987) and this controversy may actually reflect failure to distinguish PTSD from depressive sleep pathology (see below). Finally, traumatic nightmares are unique phenomena that differ from classic nightmare/ night terror Stage 4 episodes as well as from the dream anxiety attacks associated with REM sleep (Friedman, 1981; Ross *et al.*, 1989). On the one hand, PTSD dream processes are similar to REM events. Like typical REM events, they appear to the dreamer like videotape replay sequences. However, since REM sleep is associated with atonia, the nocturnal movements and panic attacks that often accompany traumatic nightmares are more similar to a State 4 nightmare/night terror attack.

In short, most physiological data support the DSM-III-R (American Psychiatric Association, 1987) and indicate that PTSD symptoms include hyperarousal, insomnia, and startle. If replicated, the results showing reduction of cortical evoked potentials may actually represent a pathophysiologic aspect of the avoidant/ numbing behaviors listed among the PTSD Category C symptoms.

Likewise, neuropharmacological and neuroendocrinological observations in PTSD patients suggest that exposure to trauma can evoke persistent biological abnormalities. Some, but not all, research findings to date indicate that PTSD may be associated with a hyperadrenergic state, hypofunctioning of the hypothalamic-pituitary-adrenocortical (HPA) axis and dysregulation of the endogenous opioid system. These findings are summarized in Table 66.2.

Pharmacological evidence for increased catecholamines is, of course, consistent with sympathetic hyperarousal noted in Table 66.1. Twenty-four-hour urinary epinephrine and norepinephrine levels in PTSD patients are significantly higher than those of normals and of patients with most other psychiatric disorders (Mason, Giller, Kosten, & Harkness, 1988; Mason, Giller, Kosten, Ostroff, & Harkness, 1986). Furthermore, PTSD patients have the highest 24-hour urinary norepinephrine/free cortisol ratio of any psychiatric diagnostic group tested to date (Mason, Giller, Kosten, & Harkness, 1988). If, as implied by this research, PTSD is associated with higher levels of circulating catecholamines. such increased adrenergic activity should desensitize or down-regulate adrenergic receptors. Indeed, this appears to be the case since the number of both alpha-2 and beta adrenergic receptor sites is reduced in platelets and lymphocytes of combat veterans with PTSD (Lerer, Garb, Siegel, & Bleich, 1986; Perry, Cella, Falkenberg, & Heidrich, 1987).

Additional evidence for central nervous system adrenergic dysregulation comes from preliminary experiments with yohimbine, an adrenergic alpha-2 antagonist that increases CNS sympathetic arousal by disinhibiting locus coeruleus activity. It is well established, that yohimbine can precipitate panic attacks in panic-

Table 66.2. Neurohumoral/Neuroendocrinological Abnormalities Associated with PTSD

Increased circulating catecholamines
↑ Urinary catecholamine levels
Down-regulation of alpha-2 and beta receptors
Hypothalamic-pituitary-adrenocortical axis abnormalities
↓ Urinary-free cortisol levels
Blunted ACTH response to CRH
Opioid system dysregulation
↓ Pain threshold at rest
Stress-induced analgesia elicited by traumatomimetic stimuli
↓ Beta-endorphin levels

One recent report found that 46% of hospitalized PTSD patients also met diagnostic criteria for MDD (Reaves, Hansen, & Whisenand, 1989). Furthermore, as mentioned previously, both PTSD and MDD are associated with alterations in both the sleep cycle and the HPA axis. Thus, much of the current confusion regarding which sleep and/or HPA abnormalities are attributable to PTSD alone or MDD (among PTSD patients) probably is due to failure to control for the presence of MDD among many patients included in the PTSD experimental group. This same argument also applies to interpretation of clinical drug trials. Future research will have to identify separate PTSD-alone and PTSD + MDD subgroups in order to determine whether antidepressant drugs have a specific anti-PTSD action or whether their usefulness in this disorder is due to their antidepressant, anxiolytic, and/or REM-suppressant actions.

In summary, there are many methodological concerns about the few controlled trials of antidepressants in PTSD. Certainly, it is premature to pass judgment about the efficacy or lack thereof of TCAs and MAOIs in PTSD. Furthermore, many psychiatrists remain convinced by their own clinical experience that antidepressants are very effective in some but not all cases of PTSD. Finally, a new report that fluoxetine is extremely effective in PTSD (Shay, 1991) joins the enthusiastic chorus of uncontrolled positive reports on the efficacy of antidepressants suggesting, at the very least, that clinical trials with this serotonin uptake inhibitor must be placed on the agenda for clinical psychopharmacological research on PTSD.

Anxiolytics

PTSD is classified in the DSM-III-R as an anxiety disorder. Although that may change in the forthcoming DSM-IV, the current classification is based on the fact that PTSD patients exhibit symptoms, such as anxiety, fear, autonomic arousal, irritability, and insomnia, that accompany most anxiety disorders. In certain respects, PTSD appears most similar to panic disorder because (1) episodic surges of anxiety (especially following exposure to traumatomimetic stimuli) resemble panic attacks, (2) avoidant behavior may become phenomenologically similar to phobic avoidance or agoraphobic withdrawal, and (3) because PTSD flashbacks meet the DSM-III-R criteria for panic attacks (Mellman & Davis, 1985).

For these reasons, one might expect that anxiolytic/antipanic drugs will prove efficacious in PTSD. Since MAOIs are the most potent antipanic agents, with TCAs close behind, the preceding discussion is certainly applicable in this regard. In other words, the possible effectiveness of MAOIs and TCAs in PTSD may be attributable to their antipanic/anxiolytic properties rather than to their antidepressant actions.

Other anxiolytics with reported efficacy in PTSD are sympatholytic agents, such as propranolol and clonidine, and benzodiazepines, such as diazepam and alprazolam. These drugs reduce sympathetic arousal and anxiety through several different mechanisms of action (Charney, Brier, Jathow, & Heninger, 1986; Ravaris, Friedman, & Hauri, 1986; Sheehan, 1982; Tanna, Penningroth, & Woolson, 1977; Tyrer & Lader, 1974). Given the sympathetic hyperarousal associated with PTSD (see above) and given the fact that propranolol, clonidine, and alprazolam (but not other benzodiazepines) reduce central and/or peripheral adrenergic activity, one might expect that such sympatholytic agents might prove beneficial in PTSD.

The only published controlled drug trial on any of these drugs is a small study on the efficacy of propranolol for 11 children with acute PTSD who had been physically and/or sexually abused (Famularo, Kinscherff, & Fenton, 1988). The study was an A-B-A design (off-on-off medication) in which propranolol was administered in doses up to 2.5 mg/kg/day. The children exhibited significant reductions in PTSD intrusive and arousal symptoms during the active drug phase of the experiment. Furthermore, when placebo was substituted for propranolol, all symptoms returned with the same intensity as before. In another study, an open trial with 14 Vietnam combat veterans treated with 120 to 160 mg of propranolol daily for 6 months appeared to effectively reduce PTSD symptoms, such as nightmares, intrusive recollections, hypervigilance, insomnia, startle reactions, and angry outbursts (Kolb, Burris, & Griffiths, 1984). Negative results with propranolol have been reported by Kinzie (1989) in a clinical report on treatment of PTSD in traumatized Cambodian refugees. Since published reports indicate that among clinical treatment-seeking patients, 60% to 80% of PTSD patients have a concurrent diagnosis of alcohol or drug abuse/dependency (Branchey, Davis, & Lieber, 1984; Keane *et al.*, 1988), the low abuse potential of beta-blockers such as propranolol will make them an attractive treatment option if their efficacy can be demonstrated conclusively.

There are two favorable reports on the anti-PTSD potency of clonidine, an alpha-2 adrenergic agonist that reduces central sympathetic activity through locus coeruleus inhibition. Both reports are open trials rather than controlled double-blind clinical studies. Kolb *et al.* (1984) reported that eight combat veterans had a favorable response to 0.2 to 0.4 mg/day of clonidine marked by reduced explosiveness, fewer nightmares, improved sleep, lessened startle, reduced intrusive recollections, and a general reduction in sympathetic arousal. Kinzie (1989) found that clonidine effectively lowered anxiety and autonomic arousal among Cambodian refugees with PTSD, especially when combined with tricyclic antidepressants.

Benzodiazepines are potent anxiolytics that have been prescribed widely for PTSD, despite the lack of any published controlled trials attesting to their clinical efficacy in PTSD. At one VA hospital, 71% of PTSD patients received benzodiazepines either exclusively (36%) or in combination with other drugs (Ciccone, Mazarek, Weisbrot, *et al.*, 1988). Many clinicians are extremely reluctant to offer benzodiazepines to PTSD patients, however, because of the risk of addiction/dependency among patients who already have very high rates of alcoholism and chemical abuse/dependency (Branchey *et al.*, 1984; Keane *et al.*, 1988). These cautionary remarks are especially pertinent to alprazolam (Xanax) which, because of its short half-life, is more likely to produce clinical complications such as rebound anxiety and withdrawal symptoms in addition to more general concerns about benzodiazepine addiction and dependence (Hig-

between the several biological systems affected in PTSD may rule out the possibility of a penicillin, lithium, or other magic bullet for PTSD. For example, our understanding of the vicious cycle of cholinergic subsensitivity and dopaminergic supersensitivity thought to occur in tardive dyskinesia has not led to a specific pharmacological intervention for that disorder.

Pharmacological Treatment for PTSD

From the previous discussion, it would appear that any drug that can dampen physiological hyperactivity, ameliorate the disturbed sleep/dream cycle, attenuate sympathetic hyperarousal, or reduce anxiety should be helpful in PTSD. In this regard, most psychotropic drugs that are effective in other disorders have been used in PTSD. In particular, antidepressants, both tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have reportedly ameliorated PTSD symptoms in uncontrolled clinical trials involving many patients. Unfortunately, the few published controlled trials of TCAs and MAOIs have presented mixed and modest results. The same can be said for anxiolytic agents, especially propranolol and clonidine, for which controlled studies are needed to bolster earlier enthusiastic anecdotal reports.

Despite the current paucity of evidence, however, there is growing conviction among many clinicians that pharmacotherapy is useful for PTSD and that it is only a matter of time before an effective pharmacological approach will be demonstrated.

Antidepressants

Antidepressants are a very interesting class of drugs to consider since in addition to their actions on affective disorders, they are effective anxiolytic and antipanic agents that can dampen sympathetic arousal through a variety of mechanisms (Charney, Menkes, & Heninger, 1981; Kahn, McNair, Lipman, *et al.*, 1986; Sheehan, Ballenger, & Jacobsen, 1980).

Antidepressants, especially TCAs, are becoming first-line drugs in PTSD pharmacotherapy. This finding is based on numerous uncontrolled studies and case reports asserting that TCAs and MAOIs reduce specific PTSD symptoms, such as hyperarousal, intrusive recollections, traumatic nightmares, and flashbacks. Associated symptoms, such as depression and anxiety, have also been responsive to antidepressant treatment but PTSD numbing/avoidant symptoms have generally been unaffected by these drugs (Blake, 1986; Boehnlein, Kinzie, Ben, & Fleck, 1985; Burstein, 1982; Davidson, Walker, & Kilts, 1987; Embry & Callahan, 1988; Falcon, Ryan, Chamberlain, & Curtis, 1985; Friedman, 1981, 1988, 1991; Hogben & Cornfield, 1981; Marshall, 1975; Milanes, Mack, & Dennison, 1984; Shen & Park, 1983; van der Kolk, 1987).

To date, there are three published controlled trials of TCAs and two of MAOIs. (There are actually only four separate studies since Frank, Kosten, Giller, and Dan, 1988, compared TCA, MAOI, and placebo in the same study.) Results are mixed and somewhat difficult to interpret. Frank *et al.* (1988) had the most favorable findings in an 8-week double-blind comparison of imipramine (a TCA), phenelzine (a MAOI), and placebo in 34 Vietnam combat veterans with PTSD who exhibited significant reduction in PTSD intrusion (but not avoidant) symptoms as measured with the Impact of Events (IES) Scale (Horowitz, Wilner, & Alvarez, 1979). Phenelzine was somewhat more potent than imipramine in this regard, but both were significantly superior to placebo. Davidson, Kudler, Smith, and Mahorney (1990), also using the IES to assess PTSD symptomatology, found 8 weeks of treatment with the TCA amitriptyline to be modestly but significantly superior to placebo. They also observed that depressed PTSD patients appeared to show greater remission than nondepressed patients and suggested that such improvement was most likely attributable to amitriptyline's antidepressant and anxiolytic properties rather than to a specific anti-PTSD effect. A third TCA study evaluated desipramine and placebo in a 4-week double-blind comparison and found no difference between the two groups with regard to remission of PTSD symptoms (Reist, Kauffmann, Haier, & Curtis, 1989). Finally, Shestatzky, Greenberg, and Lerer (1988) conducted a 4-week double-blind crossover comparison of phenelzine and placebo. In contrast to the positive results with phenelzine of Frank *et al.* (1988), this group reported no difference between MAOI and placebo with regard to remission of PTSD symptoms.

Obviously, more research is needed and it is necessary to invoke the usual caveats about research findings in a new field such as the need for larger clinical samples, better attention to dosage, and concern (recently expressed by Kudler, Davidson, Stein, & Erickson, 1989), about the lack of a well-validated observer-rated scale in current PTSD research. Certainly, the lack of significant differences could reflect a lack of statistical power since sample sizes in most of these experiments were small.

Kudler *et al.* (1989) have also pointed out that the two negative studies (Reist *et al.*, 1989; Shestatzky *et al.*, 1988) only carried out their drug trials for 4 weeks whereas positive results (Davidson *et al.*, 1990; Frank *et al.*, 1988) only emerged after an 8-week trial of imipramine, phenelzine, and amitryptyline, respectively.

A third methodological issue concerns the failure of Shestatzky *et al.* (1988) to demonstrate phenelzine's superiority over placebo in their 4-week double-blind crossover trial. Examination of their data, however, shows that failure to demonstrate superiority of MAOI over placebo was not because subjects were refractory to phenelzine but rather because they were extremely responsive to placebo.

Finally, failure to separate PTSD patients from PTSD + MDD (Major Depressive Disorder) patients may contribute to differences between the findings of Frank *et al.* (1988), and those in the other two TCA double-blind trials. Whereas Frank's group excluded patients with MDD from their experimental groups, both Davidson *et al.* (1987) and Reist *et al.* (1989) included relatively large numbers of MDD patients in their PTSD group. As argued elsewhere (Friedman, 1988, 1990, 1991), PTSD and MDD have many symptoms in common and patients often meet DSM-III-R criteria for both PTSD and MDD.

whom neuroleptics are specifically indicated (Mueser & Butler, 1987). Again, as mentioned above with most other drugs reviewed, there are no published controlled clinical trials of neuroleptic agents on PTSD patients.

Treatment of PTSD and Concurrent Chemical Abuse/Dependency

Alcohol and chemical abuse/dependency are very high among Vietnam veterans with war-zone-related PTSD and presumably among other traumatized groups as well. Epidemiologic data from the National Vietnam Veterans Readjustment Study indicate that among individuals currently suffering from PTSD, current and lifetime prevalence rates for alcoholism are 23% and 75%, respectively, while rates for current and lifetime drug abuse/dependency are 6% and 23% respectively (Kulka *et al.*, 1988). As one might expect, rates for alcohol or drug abuse/dependency are even higher, 60% to 80%, among clinical treatment-seeking cohorts of Vietnam veterans with PTSD (Branchey *et al.*, 1984; Keane *et al.*, 1988). Furthermore, there is a linear correlation between war-zone exposure and chemical abuse/dependency so that Vietnam veterans with higher levels of war-zone stress are more likely to exhibit chemical abuse/dependency than those who experienced lower levels of traumatic exposure (Keane *et al.*, 1988; Kulka *et al.*, 1988).

There may be a neurobiological reason for such high co-morbidity rates between PTSD and chemical abuse/dependency. The adrenergic hyperarousal and opioid dysregulation associated with PTSD may make affected individuals particularly susceptible to chemical abuse/dependency. Suppression of the adrenergic hyperarousal state with alcohol, central depressants, marijuana, or opiates should provide temporary relief to the person suffering from PTSD intrusive and hyperarousal symptoms. Moreover, reversal of the postulated opioid deficiency (Friedman, 1991; Perry *et al.*, 1987; van der Kolk *et al.*, 1985) through self-medication with heroin, methadone, or with other opiates would be expected to ameliorate intolerable PTSD symptomatology.

One may extend this line of reasoning another step and argue that once the vicious addiction-withdrawal cycle is established, PTSD patients may have even more difficulty achieving (and maintaining) abstinence than chemically dependent individuals without PTSD. This is because the rebound hyperarousal experienced by physically dependent PTSD patients undergoing withdrawal may itself trigger a conditioned emotional response associated with PTSD symptoms. Kosten and Krystal (1988), in an elegant review on this subject, proposed that withdrawal-induced hyperarousal will serve as a conditioned stimulus that elicits traumatomimetic PTSD symptoms. In other words, the routine difficulties of treating chemical dependency are multiplied by the complex risk of exacerbating PTSD symptoms during detoxification. This may be an even greater problem with opiate addicts, since heroin-like drugs may replenish a depleted endogenous opioid system in addition to reducing the adrenergic hyperarousal of PTSD.

The implications for treatment are clear. When PTSD and chemical dependency occur simultaneously, they must be treated simultaneously. Unfortunately, most (especially inpatient) treatment approaches attempt to treat the two disorders sequentially rather than simultaneously. Gatekeepers for such programs usually insist that patients undergo chemical detoxification/rehabilitation as a prerequisite for admission to inpatient treatment for their PTSD. Such an approach is doomed to failure because it fails to acknowledge programmatically that the complex self-sustaining interrelationships between intrapsychic, behavioral, and biological aspects of PTSD and concurrent chemical abuse/dependency demand a comprehensive approach. The recent establishment of Dual Diagnosis inpatient programs at several VA hospitals is a hopeful sign that more appropriate treatment alternatives are being introduced for patients with concurrent PTSD and chemical abuse/dependency.

Summary

1. PTSD appears to be associated with a unique pattern of biological abnormalities.
2. Physiological alterations associated with PTSD include hyperarousal of the sympathetic nervous system, an excessive startle reflex, a reducer pattern of cortical evoked potentials, and abnormalities in sleep and dreaming.
3. Neurohumoral and neuroendocrinological alterations in PTSD include increased adrenergic activity, hypothalamic-pituitary-adrenocortical axis abnormalities, and endogenous opioid dysregulation.
4. Methodological concerns about the current status of research on the neurobiology of PTSD include: (a) the small amount of published research findings; (b) lack of standardized protocols—future studies will have to compare baseline conditions with those provoked by physiological, pharmacological, and/or psychological stimulation; (c) failure to control for different diagnoses (e.g., depression, chemical abuse/dependency, etc.) that are frequently associated with PTSD; and (d) almost all quantitative biological research is on male combat veterans; research is needed on females with war-zone-related PTSD and on male and female survivors of other types of trauma.
5. Despite a growing body of open drug trials and clinical anecdotes, there have only been four double-blind trials of TCAs and MAOIs and one controlled trial of propranolol. Results with antidepressants and anxiolytic/antipanic agents are promising but inconclusive at this time.
6. Neurobiological alterations associated with PTSD may make affected individuals more susceptible to alcohol, opiates, and other illicit drug use. Therefore, when PTSD and chemical abuse/dependency occur simultaneously, they must be treated simultaneously.
7. Most open and controlled trials indicate that successful pharmacotherapy for PTSD generally results in attenuation of the DSM-III-R intrusive recollections and arousal symptoms. Avoidant symptoms, impacted grief, guilt, problems with intimacy, and moral pain do not appear to respond to medication. It appears, therefore, that drug treatment alone can never alleviate the

gitt, Lader, & Fonagy, 1985). Despite all these reservations, benzodiazepines in general are excellent anxiolytics and alprazolam in particular has potent anxiolytic/antipanic actions (Sheehan, 1982). Therefore, these drugs may prove effective in PTSD for carefully selected patients in whom the risk of addiction and dependence is minimal. Furthermore, from a theoretical point of view, the kindling model of PTSD (see below) offers a neurobiological argument for prescribing benzodiazepines for appropriate patients since limbic kindling is associated with increased benzodiazepine receptor binding (McNamara, Bonhaus, Shin, Crain, Gellman, & Giacchino, 1985; Morita, Okamoto, Seki, & Wada, 1985; Tietz, Gomaz, & Berman, 1985). In other words, benzodiazepines and other gamma-aminobutyric acid agonists or synergists may prove particularly useful in PTSD for well-selected patients.

Other Drugs and PTSD

Carbamazepine

Kindling is a process by which neuroanatomic structures, especially those in the limbic system, become increasingly sensitized following repeated exposure to electrical stimulation or stimulant (cocainelike) drugs. Kindling can lead progressively to profound neurophysiological abnormalities, such as grand mal seizures, or to the progressive development of aberrant behavior. Once established, kindling is a relatively stable neurobiological alteration. According to this model, chronic high intensity central sympathetic arousal mediated by the locus coeruleus kindles limbic nuclei thereby producing a stable neurobiological abnormality.

Kindling was first invoked as a neuropsychiatric model to explain lithium-refractory bipolar affective disorder by Post and Kopanda (1976). They suggested that carbamazepine (Tegretol) be prescribed for this disorder because it is an anticonvulsant that effectively counters the neurobiological changes produced by kindling. Likewise, van der Kolk (1987) and Friedman (1988) independently hypothesized that the chronic CNS sympathetic arousal associated with PTSD produces an endogenous state that optimizes the conditions for limbic kindling. Furthermore, a kindling model explains the well-known clinical fact that PTSD is extremely stable—if untreated it can persist for decades (Archibald & Tuddenham, 1965; Kluznik, Speed, van Valkenburg, & Magraw, 1986).

Motivated by such a theoretical perspective, two groups have conducted open clinical trials of carbamazepine in Vietnam combat veterans with chronic PTSD. Lipper, Davidson, Grady, *et al.* (1986) reported reduced intrusive symptoms, such as traumatic nightmares, flashbacks, and intrusive recollections. Wolf, Alavi, and Mosmaim (1988) observed alleviation of impulsivity, irritability, and violent behavior in 10 combat veterans with PTSD. Whereas Lipper's group assessed carbamazepine's effect on PTSD intrusive and avoidant symptoms, Wolf's group did not monitor specific PTSD symptoms; therefore, their positive results could be due to carbamazepine's attenuation of anger and rage (Eichelman, 1988) rather than to an anti-PTSD effect. From a different perspective, however, it is noteworthy that all patients in the Wolf *et al.* (1988) study had normal EEGs and no evidence of temporal lobe epilepsy. Therefore, since the Wolf *et al.* patients definitely did not suffer from a PTSD-like syndrome caused by complex partial seizures as proposed by others (Greenstein, Kitchner, & Olsen, 1986; Stewart & Bartucci, 1986), the positive results with carbamazepine cannot be attributed to a traditional anticonvulsant effect and may instead reflect specific anti-PTSD potency for this drug.

Lithium

There are uncontrolled clinical reports that lithium is an effective treatment for PTSD, even for patients without a personal or family history of bipolar affective disorder or cyclothymia (Kitchner & Greenstein, 1985; van der Kolk, 1983). Van der Kolk (1987) reported that 14 out of 22 PTSD patients treated with lithium exhibited diminished sympathetic arousal, a decreased tendency to react to stress as if it were a recurrence of their original trauma, and reduced alcohol intake. He has stated that the clinical response to lithium in his PTSD patients was "clinically indistinguishable" from the response to carbamazepine, as was described in the previous paragraph. As with most other reports of pharmacological efficacy in PTSD, there are no published systematic double-blind trials of lithium in PTSD.

Neuroleptics

It is not difficult to understand why neuroleptics were widely prescribed during the 1960s and 1970s for Vietnam war zone veterans who presented clinically with behavioral problems and/or psychotic symptoms. During the pre-DSM-III (American Psychiatric Association, 1980) era, PTSD did not exist as a classifiable psychiatric diagnosis to the average psychiatrist. At that time (what we would now call) unrecognized PTSD sometimes appeared to be a bizarre and explosive psychotic disorder marked by agitation, paranoid thoughts, loss of control, potential for violence, and brief psychotic episodes, which are now called *PTSD flashbacks*. Therefore, neuroleptics frequently were prescribed as the drug of choice for such patients.

Since then, we have learned that adrenergic hyperarousal, intrusive recollections, avoidant/numbing behavior, and reactivity to traumatomimetic stimuli are the primary target symptoms of PTSD rather than psychotic thinking. Currently, antidepressants and anxio-lytic/antipanic agents show the greatest promise as first-line drugs for PTSD. After two decades of misuse and overuse of antipsychotic agents, it is now apparent that neuroleptics have no place in the routine treatment of PTSD.

Although neuroleptics should never be prescribed until other agents have been tried, they do have a role in the treatment of refractory PTSD marked by paranoid behavior, aggressive psychotic symptoms, overwhelming anger, fragmented ego boundaries, self-destructive behavior, and frequent flashback episodes marked by frank auditory and visual hallucinations of traumatic episodes (Atri & Gilliam, 1989; Friedman, 1981, 1991; Walker, 1982). It has been suggested that PTSD patients with auditory hallucinations constitute a distinct subgroup for

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suffering in this disorder. At this time, pharmacotherapy appears to be primarily useful as an adjunct to psychological (intrapsychic and/or behavioral) treatment of PTSD.

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